1(01

PCT/EP00/0

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 26 June 2001 (26.06.01)	
International application No. PCT/EP00/09750	**Applicant's or agent's file reference** SCB586PCT
International filing date (day/month/year) 05 October 2000 (05.10.00)	**Priority date** (day/month/year) 08 October 1999 (08.10.99)
Applicant GESSA, Gian, Luigi et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

03 May 2001 (03.05.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

EP0009750

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB586PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/09750	05/10/2000	08/10/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant NEUROSCIENZE S.C.A.R.L., et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/05/2001	11.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Langer, A Telephone No. +49 89 2399 7809

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09750

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15 as originally filed

Claims, No.:

1,2 as received on 21/12/2001 with letter of 20/12/2001

Drawings, sheets:

1/2,2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1
	No:	Claims 2
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-2
Industrial applicability (IA)	Yes:	Claims 1-2
	No:	Claims

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Art. 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents. If not indicated otherwise, the relevant passages are those cited in the international search report.

D1: BROADBENT J ET AL: 'Differential effects of GABA(A) and GABA(B) agonists on sensitization to the locomotor stimulant effects of ethanol in DBA/2 J mice.' PSYCHOPHARMACOLOGY, (1999 JAN) 141 (2) 197-205. , XP000965275

D2: HUMENIUK R E ET AL: 'The role of GABAB receptors in mediating the stimulatory effects of ethanol in mice.' PSYCHOPHARMACOLOGY, (1993) 111 (2) 219-24. , XP001036573

D3: BOISMARE F ET AL: 'ARE GAMMA AMINOBUTYRIC-ACID-ERGIC RECEPTORS INVOLVED IN THE VOLUNTARY INTAKE OF ETHANOL BY THE RAT.' ASSOCIATION FRANCAISE DES PHARMACOLOGISTES (FRENCH ASSOCIATION OF PHARMACOLOGISTS) FRANCO-ITALIAN MEETING OF PHARMACOLOGISTS, PARIS, FRANCE, JUNE 7-8, 1984. J PHARMACOL (PARIS). (1984 (RECD 1985)) 15 (4), 457-458. , XP001036594

D4: FILE S E ET AL: 'BACLOFEN REVERSES THE SIGNS OF ETHANOL WITHDRAWAL IN RATS.' MEETING OF THE BRITISH PHARMACOLOGICAL SOCIETY, SHEFFIELD, ENGLAND, UK, APRIL 18-20, 1990. BR J PHARMACOL. (1990) 100 (PROC SUPPL JUNE), 340P. , XP001036582

D5: DAOUST M ET AL: 'GABA transmission, but not benzodiazepine receptor stimulation, modulates ethanol intake by rats.' ALCOHOL, (1987 NOV-DEC) 4 (6) 469-72. , XP001036617

D6: KUZIEMKA-LESKA M ET AL: 'Baclofen and AII 3-7 on learning and memory processes in rats chronically treated with ethanol.' PHARMACOL., BIOCHEM. BEHAV., (1998). VOL. 62, NO. 1, PP. 39-43. CODEN: PBBHAU. ISSN. 0091-3057., XP001035246 Department of Pharmacology, Medical University in Bialystok, Bialystok

D7: FILE S E ET AL: 'Effects of baclofen and nitrendipine on ethanol withdrawal

responses in the rat.' NEUROPHARMACOLOGY, (1991 FEB) 30 (2) 183-90. , XP001036625

D8: COLOMBO G ET AL: 'Ability of baclofen in reducing alcohol intake and withdrawal severity: I--Preclinical evidence.' ALCOHOLISM, CLINICAL AND EXPERIMENTAL RESEARCH, (2000 JAN) 24 (1) 58-66. , XP001036700

D9: ADDOLORATO G ET AL: 'Ability of baclofen in reducing alcohol craving and intake: II--Preliminary clinical evidence.' ALCOHOLISM, CLINICAL AND EXPERIMENTAL RESEARCH, (2000 JAN) 24 (1) 67-71. , XP001036708

D10: COLOMBO, G. (1) ET AL: 'Ability of baclofen in reducing alcohol intake in alcohol -preferring sP rats and withdrawal severity in alcohol - dependent rats.' ALCOHOLISM CLINICAL AND EXPERIMENTAL RESEARCH, (MAY, 2000) VOL. 24, NO. 5 SUPPLEMENT, PP. 37A. PRINT. MEETING INFO.: SCIENTIFIC MEETING OF THE RESEARCH SOCIETY ON ALCOHOLISM SANTA BARBARA, CALIFORNIA, USA JUNE 24-29, 2000 RESEARCH SOCIETY ON ALCOHOLI, XP001036738

The priority document was not available for evaluation of the present application. The P-documents D8-D10 are therefore ignored for the preliminary examination. However, If the priority claimed was not valid, these documents would be relevant for the evaluation of novelty of claims 1 and 2.

2. Novelty and Inventive Step (Art. 33 (2) (3) PCT)

For the evaluation of the present claims it has to be taken into account that sensitization for alcohol has been accorded a central role in addiction (document D1, introduction). Any drug treating sensitization is therefore considered to treat alcoholism.

For the evaluation of claim 2 it has to be particularly taken into account that under the PCT the indicated use of a pharmaceutical composition cannot confer novelty to that composition.

The technical features of **claim 2** are disclosed by documents D1-D7 (abstracts). This claim therefore lacks novelty and inventive skill in terms of Art. 33 (2) (3) PCT.

Since documents D1-D7 relate to animal experiences only, **claim 1** is considered to be novel over the prior art cited.

The claim however lacks inventive skill in terms of Art. 33 (3) PCT for the following reasons:
Even though animal experiences are known to provide only limited predictability for the corresponding effects in humans, it is common practice to draw conclusions for the treatment of humans out of such animal experiences. Furthermore, documents D5 and D7 (first paragraph of introduction) situate the performed rodent experiences in the context of human alcoholism, thereby indicating that the published results are finally intended to provide solutions for the treatment of humans. The skilled person would therefore transfer the disclosure of documents D1-D7 to the field of human alcoholism with a reasonable expectation of success.

3. Industrial Applicability (Art. 33 (4) PCT)

For the assessment of the present **claims 1 and 2** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/26638 A3

(51) International Patent Classification[7]: A61K 31/197, A61P 25/32

(21) International Application Number: PCT/EP00/09750

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A002107 8 October 1999 (08.10.1999) IT

(71) Applicant *(for all designated States except US)*: **NEUROSCIENZE S.C. A R.L.** [IT/IT]; Via Palabanda, 9, I-09125 Cagliari (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GESSA, Gian, Luigi** [IT/IT]; Via Palabanda, 9, I-09125 Cagliari (IT). **COLOMBO, Giancarlo** [IT/IT]; Centro CNR per la Neurofarmacologia, Dipartimento di Neuroscienze "B.B. Brodie", Via Porcell, 4, I-09124 Cagliari (IT). **ADDOLORATO, Giovanni** [IT/IT]; Istituto di Medicina Interna, Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8, I-00168 Roma (IT).

(74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milan (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
28 February 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/26638 A3

(54) Title: THE USE OF BACLOFEN IN THE TREATMENT OF ALCOHOLISM

(57) Abstract: The use of baclofen for the treatment of alcohol withdrawal syndrome and promotion of abstinence in alcoholics.

INTERNATIONAL SEARCH REPORT

Inte[illegible]plication No
PC[illegible]/09750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/197 A61P25/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, BIOSIS, CHEM ABS Data, WPI Data, PAJ, EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BROADBENT J ET AL: "Differential effects of GABA(A) and GABA(B) agonists on sensitization to the locomotor stimulant effects of ethanol in DBA/2 J mice." PSYCHOPHARMACOLOGY, (1999 JAN) 141 (2) 197-205. , XP000965275 the whole document ---	1,2
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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2001	21/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Gac, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	FILE S E ET AL: "BACLOFEN REVERSES THE SIGNS OF ETHANOL WITHDRAWAL IN RATS." MEETING OF THE BRITISH PHARMACOLOGICAL SOCIETY, SHEFFIELD, ENGLAND, UK, APRIL 18-20, 1990. BR J PHARMACOL. (1990) 100 (PROC SUPPL JUNE), 340P. , XP001036582 the whole document	2
X	DAOUST M ET AL: "GABA transmission, but not benzodiazepine receptor stimulation, modulates ethanol intake by rats." ALCOHOL, (1987 NOV-DEC) 4 (6) 469-72. , XP001036617 the whole document	1
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
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   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/05/2001	11.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Langer, A Telephone No. +49 89 2399 7809

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09750

I. Basis f the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
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1-15	as originally filed				

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Drawings, sheets:

1/2,2/2	as originally filed

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1
	No:	Claims 2
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-2
Industrial applicability (IA)	Yes:	Claims 1-2
	No:	Claims

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Art. 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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D4: FILE S E ET AL: 'BACLOFEN REVERSES THE SIGNS OF ETHANOL WITHDRAWAL IN RATS.' MEETING OF THE BRITISH PHARMACOLOGICAL SOCIETY, SHEFFIELD, ENGLAND, UK, APRIL 18-20, 1990. BR J PHARMACOL. (1990) 100 (PROC SUPPL JUNE), 340P. , XP001036582

D5: DAOUST M ET AL: 'GABA transmission, but not benzodiazepine receptor stimulation, modulates ethanol intake by rats.' ALCOHOL, (1987 NOV-DEC) 4 (6) 469-72. , XP001036617

D6: KUZIEMKA-LESKA M ET AL: 'Baclofen and AII 3-7 on learning and memory processes in rats chronically treated with ethanol.' PHARMACOL., BIOCHEM. BEHAV., (1998). VOL. 62, NO. 1, PP. 39-43. CODEN: PBBHAU. ISSN. 0091-3057., XP001035246 Department of Pharmacology, Medical University in Bialystok, Bialystok

D7: FILE S E ET AL: 'Effects of baclofen and nitrendipine on ethanol withdrawal

responses in the rat.' NEUROPHARMACOLOGY, (1991 FEB) 30 (2) 183-90. , XP001036625

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The priority document was not available for evaluation of the present application. The P-documents D8-D10 are therefore ignored for the preliminary examination. However, If the priority claimed was not valid, these documents would be relevant for the evaluation of novelty of claims 1 and 2.

2. Novelty and Inventive Step (Art. 33 (2) (3) PCT)

For the evaluation of the present claims it has to be taken into account that sensitization for alcohol has been accorded a central role in addiction (document D1, introduction). Any drug treating sensitization is therefore considered to treat alcoholism.

For the evaluation of claim 2 it has to be particularly taken into account that under the PCT the indicated use of a pharmaceutical composition cannot confer novelty to that composition.

The technical features of **claim 2** are disclosed by documents D1-D7 (abstracts). This claim therefore lacks novelty and inventive skill in terms of Art. 33 (2) (3) PCT.

Since documents D1-D7 relate to animal experiences only, **claim 1** is considered to be novel over the prior art cited.

The claim however lacks inventive skill in terms of Art. 33 (3) PCT for the following reasons:
Even though animal experiences are known to provide only limited predictability for the corresponding effects in humans, it is common practice to draw conclusions for the treatment of humans out of such animal experiences. Furthermore, documents D5 and D7 (first paragraph of introduction) situate the performed rodent experiences in the context of human alcoholism, thereby indicating that the published results are finally intended to provide solutions for the treatment of humans. The skilled person would therefore transfer the disclosure of documents D1-D7 to the field of human alcoholism with a reasonable expectation of success.

3. Industrial Applicability (Art. 33 (4) PCT)

For the assessment of the present **claims 1 and 2** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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MI99A002107 8 October 1999 (08.10.1999) IT

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GESSA, Gian, Luigi** [IT/IT]; Via Palabanda, 9, I-09125 Cagliari (IT). **COLOMBO, Giancarlo** [IT/IT]; Centro CNR per la Neurofarmacologia, Dipartimento di Neuroscienze "B.B. Brodie", Via Porcell, 4, I-09124 Cagliari (IT). **ADDOLORATO, Giovanni** [IT/IT]; Istituto di Medicina Interna, Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8, I-00168 Roma (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milan (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/26638 A3

(54) Title: THE USE OF BACLOFEN IN THE TREATMENT OF ALCOHOLISM

(57) Abstract: The use of baclofen for the treatment of alcohol withdrawal syndrome and promotion of abstinence in alcoholics.

INTERNATIONAL SEARCH REPORT

Inte[redacted] Application No
PC[redacted]00/09750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/197 A61P25/32

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2001	21/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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INTERNATIONAL SEARCH REPORT

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SCB586PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 09750	05/10/2000	08/10/1999
Applicant		
NEUROSCIENZE S.C.A.R.L.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

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2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

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   THE USE OF BACLOFEN IN THE TREATMENT OF ALCOHOLISM

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6. The figure of the **drawings** to be published with the abstract is Figure No.

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   [ ] because the applicant failed to suggest a figure.

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   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/09750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/197 A61P25/32

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PATENT COOPERATION TREATY

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Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	ADDOLORATO G ET AL: "Ability of baclofen in reducing alcohol craving and intake: II--Preliminary clinical evidence." ALCOHOLISM, CLINICAL AND EXPERIMENTAL RESEARCH, (2000 JAN) 24 (1) 67-71. , XP001036708 the whole document ---	1,2
P,X	COLOMBO, G. (1) ET AL: "Ability of baclofen in reducing alcohol intake in alcohol -preferring sP rats and withdrawal severity in alcohol - dependent rats." ALCOHOLISM CLINICAL AND EXPERIMENTAL RESEARCH, (MAY, 2000) VOL. 24, NO. 5 SUPPLEMENT, PP. 37A. PRINT. MEETING INFO.: SCIENTIFIC MEETING OF THE RESEARCH SOCIETY ON ALCOHOLISM SANTA BARBARA, CALIFORNIA, USA JUNE 24-29, 2000 RESEARCH SOCIETY ON ALCOHOLI, XP001036738 the whole document -----	1,2

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(54) Title: THE USE OF BACLOFEN IN THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME AND TO PROMOTE ALCOHOL ABSTINENCE IN ALCOHOLICS

(57) Abstract: The use of baclofen for the treatment of alcohol withdrawal syndrome and promotion of abstinence in alcoholics.

THE USE OF BACLOFEN IN THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME AND TO PROMOTE ALCOHOL ABSTINENCE IN ALCOHOLICS

The present invention relates to the use of Baclofen in the treatment of alcohol withdrawal syndrome and promotion of abstinence in alcoholics.

TECHNOLOGICAL BACKGROUND

Alcoholism is a serious medical, social and economic problem facing almost all human societies worldwide. Alcoholism has been diagnosed in an estimated 5% of adult population in the Western countries, while a larger number of people have been classified as problem drinkers (i.e. people who drink alcohol at a level that is risky for their health). Medical interventions in the field of alcoholism are primarily aimed at a) relieving the consequences of alcohol withdrawal syndrome and b) arresting alcohol drinking, maintaining sobriety for as long as possible. Pharmacotherapy is conceived to provide a substantial contribution to these goals, facilitating the psychological support and social rehabilitation of alcoholic patients.

Several pharmacological substances acting on neurotransmitter systems affected by the action of alcohol have been studied, naltrexone (Volpicelli et al., 1992; O' Malley et al., 1992), acamprosate (Withworth et al, 1996), fluoxetine (Naranjo et al, 1994), may be mentioned, inter alia. Furthermore, gamma-hydroxybutyric acid (GHB) a compound with behavioral GABA-like effects (Colombo et al., 1998), proved able to decrease alcohol intake in rats (Agabio et al., 1998) and humans (Gallimberti et al., 1992) and to induce alcohol abstinence in alcoholics (Addolorato et al., 1996; 1998a; 1998b). In addition, GHB proved to be effective in treating alcohol withdrawal syndrome both in

experimental animals (Gessa et al., 2000) and humans (Gallimberti et al., 1989), with a similar efficacy to diazepam (Addolorato et al., 1999b). It has been hypothesized that the effects of GHB on alcohol intake, craving and withdrawal syndrome are related to its alcohol-mimicking effect on the CNS (Colombo et al., 1995).

Baclofen, (beta-(4-chlorophenyl)-gamma-aminobutyric acid), a lipophilic derivative of GABA, is a potent and stereoselective $GABA_B$ receptor agonist. At present it is used clinically to control spasticity (Davidoff, 1985).

Baclofen has already been tested in experimental animals to evaluate its capacity to induce a selective reduction of daily alcohol intake in Long Evans rats (Daoust et al., 1987); on the other hand, subsequent studies reported that a higher dose of baclofen stimulated daily alcohol intake during both acquisition (Smith et al., 1992) and maintenance (Smith et al., 1999) phases of alcohol drinking behaviour in Long Evans rats; finally, central administration of baclofen failed to alter alcohol intake in Wistar rats (Tomkins and Fletcher, 1996). With regard to alcohol withdrawal syndrome, File and colleagues (1991) reported that small doses of baclofen reduced the anxiety-like behaviours and tremors associated with alcohol withdrawal syndrome in alcohol-dependent rats; however, no effects on alcohol withdrawal tremors after baclofen administration were observed in mice (Humeniuk et al., 1994) and rhesus monkeys (Tarika and Winger, 1980).

Therefore, it was not possible to envisage a therapeutic effect of baclofen in the treatment of alcoholism on the basis of the aforementioned studies.

DISCLOSURE OF THE INVENTION

Based on the clinical evidence available and on results obtained with reliable experimental models, it has

been observed that baclofen may be successfully used in the treatment of alcoholism.

In the present invention, "baclofen" is intended as all baclofen stereoisomers as well as the mixtures thereof.

The results obtained by means of the present invention allow the overcoming of uncertainties as to inconsistencies and discrepancies in the above data which, when considered as a whole, made baclofen appear unsuitable for the specific aims.

Baclofen activity has been evidentiated in both a clinical study, as well as in Wistar rats previously rendered physically dependent on alcohol by the repeated administration of intoxicating doses of alcohol. Similar findings have been obtained using *Sardinian alcohol-preferring* (sP) rats, which are a predictive, reliable experimental model.

Accordingly, baclofen will be administered to alcoholic patients at daily dosages ranging from 10 to 50 mg, preferably from 15 to 30 mg, using conventional pharmaceutical compositions, preferably pharmaceutical compositions suited to oral administration.

The drug will be administered once or more times daily, and may be protracted for several weeks (for example, 3 to 6 weeks or more), in view of the fact that baclofen is well tolerated, is not toxic and does not induce addiction phenomena.

The invention will be now described in greater detail in the following Examples.

Example 1: Effect of baclofen on alcohol withdrawal syndrome

Animals

Male Wistar rats (Charles River, Calco, CO, Italy), weighing 275-300 g were used. After delivery, rats were

left undisturbed for 7 days to acclimatize to new housing conditions. Animals were housed 5 per cage with wood chip bedding under an artificial light-dark cycle of 12/12 hr (light on at 7:00 hr), at a constant temperature of 22±2°C and relative humidity of 60%. Rats were given free access to water and standard laboratory food (MIL Morini, San Polo d'Enza, RE, Italy) throughout the entire experiment.

Intoxication procedure

Rats were rendered physically dependent on alcohol by the method of Majchrowicz (1975). This consisted of 4 daily administrations of alcohol solution (20% w/v, in tap water) by intragastric gavage for 6 consecutive days, in order to maintain constant blood alcohol concentrations. Alcohol was administered at 6:00, 12:00, 18:00 and 24:00 hr. At the initial administration of the treatment, 4 g/kg alcohol were given to all rats. The assessment of subsequent doses was determined individually for each rat at the above administration times on the basis of the observed degree of intoxication using the intoxication-dose relationship conceived by Majchrowicz (1975). Six successive stages of intoxication were defined: neutrality, sedation, ataxia 1, 2 and 3, loss of righting reflex. Alcohol doses, ranging from 0 to 5 g/kg, were inversely related to the degree of intoxication. Assessment of the degree of intoxication and of the alcohol dose was decided by operators trained for the same evaluation criteria.

Rats were weighed once a day (at 9:00 hr). During chronic alcohol treatment, rats spent most of the time in a severe state of intoxication, unable to eat by themselves. Therefore, the loss in body weight was partially compensated by the daily oral administration (at 9:00 hr) of 20 g/kg liquid diet (Isomil, M&R, Zwolle, The

Netherlands).

Withdrawal assessment

Intensity of alcohol withdrawal signs was evaluated in each rat scoring a) spontaneous behaviour in its home cage for 10 sec, and then b) response to handling. Eleven separate items were scored using a 4-point scale (0 to 3, paralleling increased frequency of occurrence and degree of severity of items), modified from a scale described by Lal et al. (1988). The following items were rated: general activity, shakes, jerks, general tremors, head tremors, tail tremors, rigidity of muscle tone, tail rigidity, bracing posture, vocalization and spontaneous convulsions. The sum of the 11 values was the total score assigned to each rat on each observation. Scores of 8 to 9 indicated a neutrality state, corresponding to healthy and undrugged rats. Observation and scoring were carried out on a blind basis. Between observations, rats were left undisturbed in their home cage.

Experimental design

Observations and scoring were carried out every hour for 11 consecutive hours starting at 15-hr after the last alcohol administration. Prior to beginning the observation and scoring, rats were randomly assigned to 4 groups of n=8 subjects each. Animals which convulsed prior to drug administration were excluded from the study. Baclofen [(±)-baclofen; Sigma Chemical Co., St. Louis, MO, USA] was dissolved in saline (added with a few drops of a 0.1N HCl solution) and injected ip at the doses of 0, 10, 20 and 40 mg/kg (injection volume: 10 ml/kg) immediately after the 15-hr observation period.

Two separate groups of rats received 0 (n=8) and 20 (n=9) mg/kg baclofen, dissolved and injected as described above, 16 hours after the last alcohol administration. One

hour later, these rats were tested for susceptibility to audiogenic seizures, being placed in a cylindrical box of 60 cm diameter and exposed to 30-sec key shaking.

Statistical analyses

Statistical evaluation of the daily amount of alcohol administered and the loss of rat body weight in each rat group was performed by one-way ANOVAs in the study testing the effect of baclofen on the intensity of alcohol withdrawal signs, and Mann-Whitney tests in the study testing the effect of baclofen on susceptibility to audiogenic seizures. Data concerning the effects of baclofen on the intensity of alcohol withdrawal signs were analyzed by a two-way (baclofen dose X time interval) ANOVA with repeated measures on time intervals, followed by the Newman-Keuls test in order to test group differences. Occurrence of audiogenic seizures was evaluated by means of Fisher's Exact test for a 2X2 Table [treatment (vehicle, baclofen) X seizure (presence, absence)].

Results

Rats assigned to the various experimental groups did not differ in daily alcohol intake and loss of body weight during alcohol treatments. The average daily dose of alcohol administered was 9.7±0.3, 9.9±0.3, 9.9±0.4 and 10.1±0.4 g/kg [mean ± S.E.M.; $F(3;188)=0.2858$, $P>0.05$] in the rat groups receiving 0, 10, 20 and 40 mg/kg baclofen, respectively, in the study testing baclofen effect on the intensity of alcohol withdrawal signs, and 10.0±0.3 and 9.9±0.3 g/kg [mean ± S.E.M.; $P>0.05$ (Mann-Whitney test)] in the rat group receiving 0 and 20 mg/kg baclofen, respectively, in the study testing baclofen effect on susceptibility to audiogenic seizures. The average percentage of weight loss was 20.4±1.6, 19.0±0.7, 20.4±1.7 and 18.8±1.1 [mean ± S.E.M.; $F(3;28)=0.4376$, $P>0.05$] in the

rat groups receiving 0, 10, 20 and 40 mg/kg baclofen, respectively, in the study testing baclofen effect on the intensity of alcohol withdrawal signs, and 20.0±1.2 and 19.5±1.3 [mean ± S.E.M.; P>0.05 (Mann-Whitney test)] in the rat group receiving 0 and 20 mg/kg baclofen, respectively, in the study testing baclofen effect on susceptibility to audiogenic seizures.

Baclofen administration resulted in a dose-dependent, significant reduction of the intensity of alcohol withdrawal signs in alcohol-dependent rats [$F_{dose}(4;350)=8.04$, $P<0.0005$] (Fig. 1). The *post-hoc* test indicated that reduction of alcohol withdrawal score lasted for 2, 6 and 7 hrs after drug administration in the rat groups treated with 10, 20 and 40 mg/kg baclofen, respectively. The highest dose tested (40 mg/kg) induced a marked degree of muscle relaxation and sedation, as shown by a withdrawal score lower than that obtained for healthy and undrugged rats. In contrast, at the dose of 20 mg/kg baclofen, no profound muscle flaccidity and loss of vigilance were observed, and the withdrawal score approached the neutrality-state set for 4-5 hours.

A dose of 20 mg/kg baclofen significantly ($P<0.05$, Fisher's Exact test) protected rats against audiogenic seizures. Indeed, 8 out of 8 rats in the vehicle-treated group and 5 out of 9 rats in the baclofen-treated group exhibited seizures after exposure to *key shaking*.

Example 2: Effect of baclofen on voluntary alcohol intake

Animals

Male sP rats, from the 42nd generation and approximately 6 months old, were used. Rat body weight ranged between 450 and 600 g. Rats were individually housed in standard plastic cages with wood chip bedding. The

animal facility was under a reverse, artificial 12/12 hr light-dark cycle (light on at 21:00 hr), at a constant temperature of 22±2°C and relative humidity of 60%. Food pellets (MIL Morini, San Polo d'Enza, RE, Italy) were always available.

Alcohol drinking procedure

Alcohol (10% v/v, in tap water) and tap water were offered under the two-bottle free choice regimen with unlimited access 24 hr/day. Bottles were refilled every day with fresh solution and their position interchanged at random to avoid development of position preference. Alcohol and water intakes were recorded daily, immediately before lights off. All rats used in the present study fulfilled the selection criteria adopted in this laboratory to qualify as sP rats (Colombo, 1997). Rats were habituated to handling, ip injection and frequent removal of bottles.

Rats were divided into 4 groups (n=7) matched for alcohol and water intakes over the 3 days preceding the start of drug treatment. Baclofen [(±)-baclofen; Sigma Chemical Co., St. Louis, MO, USA] was dissolved in 4 ml/kg saline and injected ip at the doses of 0, 2.5, 5 and 10 mg/kg once a day (20 to 30 min prior to light off) for 14 consecutive days. Alcohol, water and food intakes were monitored daily at 8:00-9:00 hr.

Data Analyses

Data on baclofen effect on alcohol intake (expressed in g/kg), water intake (ml/kg), total fluid intake (ml/kg), food intake (g/kg) and preference ratio (percentage of alcohol solution consumed over total fluid intake) were analyzed by two-way (baclofen dose X days of treatment) ANOVAs with repeated measures on "treatment days". When appropriate, ANOVAs were followed by the Newman-Keuls test for post-hoc comparisons.

Results

The repeated daily administration of baclofen induced a dose-dependent reduction of voluntary alcohol intake in sP rats [$F_{dose}(3;312)=6.20$, $P<0.005$] (Fig. 2, panel A). The magnitude of the reduction, compared to saline-treated rats and calculated over the entire treatment period, averaged approximately 10, 20 and 30% in the 2.5, 5 and 10 mg/kg baclofen-dosed rats. A dose-dependent, significant increase in water intake in baclofen-treated rat groups [$F_{dose}(3;312)=5.12$, $P<0.01$] (Fig. 2, panel B) compensated the reduction in alcohol consumption and left total fluid intake virtually unchanged [$F_{dose}(3;312)=1.30$, $P>0.05$] (Fig. 2, panel C). The preference ratio between alcohol solution and water consumed in baclofen-treated groups reflected the changes monitored in alcohol and water consumption [$F_{dose}(3;312)=6.13$, $P<0.005$] (data not shown). Finally, ANOVA revealed a significant effect of baclofen also on food intake [$F_{dose}(3;312)=4.91$, $P<0.01$]; however, as shown in Fig. 2, panel D, the reducing effect of baclofen was limited to the highest dose tested and to the first half of the treatment period. When baclofen administration was discontinued, both alcohol and water intakes returned immediately to control levels (Fig. 2).

Example 3: clinical tests

A total of 10 male patients of mean age: 44.0±10.1 yrs with current alcoholism according to DSM IV criteria by American Psychiatric Association (1944) were studied. Baclofen was orally administered for 4 weeks, at the dose of 15 mg/day refracted in 3 times/day for the first 3 days, increasing the dose to 30 mg/day refracted in 3 times/day for the remaining 27 days.

The effects of the treatment were evaluated by the Alcohol Craving Scale (ACS) at the start of the study (T0)

and subsequently on a weekly basis until completion of treatment. (T1 – T4). ACS is a questionnaire containing 11 items, each of which requires a yes or no answer, corresponding to 1 or 0 points, respectively, and 3 multiple choice questions, to which a score of 1 is attributed for affirmative answers; the maximum craving score was therefore 14 (Gallimberti et al, 1992; Addolorato et al, 1998b). Moreover abstinence from alcohol was evaluated on the basis of the patient's self-evaluation and of family member interview, and determination of blood alcohol concentration and of alcohol in saliva by QED (Enzymatics Inc., Horsham, UK) at each outpatient control, and on the basis of the main biological markers of alcohol abuse (aspartate aminotransferase-AST-, alanine aminotransferase-ALT-, gamma glutamyltranspeptidase-GGT-, mean cellular volume-MCV-) performed at the start and at the end of the study. Finally a self-reported alcohol intake was recorded as the mean number of standard drinks consumed per day (one standard drink = 12 grams of absolute alcohol) (Secretary of Health and Human Services, 1997).

Results

Of the ten individuals recruited, one dropped out and was therefore excluded from the statistical analysis. Of the nine who completed the study, two continued to drink alcohol, although they substantially reduced their daily drinks from the first week of treatment (namely, the median value of their daily drinks was reduced from 8, as recorded prior to the start of the treatment, to 2, and then remained stable throughout the experimental period. Remarkably, the other seven subjects achieved and maintained a complete abstinence throughout the experimental period.

Baclofen was revealed as being effective in reducing

alcohol craving from the first week of drug administration (ACS median score and [range]: T0: 9 [3-14] vs. T1: 3 [0-8]; $p<0.01$); subsequently the ACS median value was stable at the different times of observation (table).

No notable difference in ACS median score was found between the abstinent patients and subjects who continued to drink at any time evaluated (table).

The most common sensation reported by patients was the disappearance of obsessive thinking about alcohol after a few days of baclofen administration. Obsessive thinking refers to a mental state in which alcoholic patients, especially in the first stage of treatment, have a constant internal dialogue about whether to use alcohol or to resist. One of these patients had experienced GHB anti-craving effects several years previously, but reported no change in his obsessive thoughts about alcohol with GHB therapy.

Comparison of laboratory data obtained both prior to and following baclofen administration, a significant decrease in values of GGT (T0: 71.7 ± 44.2 U/l vs T4: 31.2 ± 18.0 U/l, $p<0.01$), of AST (T0: 54.7 ± 13.4 U/l vs T4: 23.5 ± 10.0 U/l, $p<0.01$), ALT (T0: 55.1 ± 17.4 U/l vs T4: 21.7 ± 10.2 U/l, $p<0.01$) and MCV (T0: 96.3 ± 3.4 $\mu\mu^2$ vs T4: 93.6 ± 2.4 $\mu\mu^2$, $p<0.01$) was found.

As far as side-effects are concerned, no serious systemic or single-organ events leading to drug cessation were reported and no patients discontinued the drug. In one patient the daily dose of the drug was reduced to 15 mg per day from the 2nd week of treatment due to headache, difficulty in concentrating, lack of appetite and sedation. Tolerability was fair in all patients. No patients referred euphoria or other pleasant effects caused by the drug. No subjects showed craving for the drug; at drug

discontinuation, no drug withdrawal syndrome or side effects due to drug suspension was observed.

Table

Patients	No	T0	T1	T2	T3	T4	
Whole group	9	9 (3-14)	3 (0-6)*	1 (0-6)*	1 (0-4)*	0 (0-4)*	
Group A	7	8 (3-14)	3 (0-8)*	1 (0-6)*	1 (0-4)*	0 (0-4)*	
Subject 1		9	2	3	2	2	
Subject 2		14	8	6	4	4	

Group A: abstinent subjects during the experiment period; Subjects 1 and 2: non abstinent subjects during the experiment period; * p<0,01 vs T0.

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CLAIMS

1. The use of baclofen or any stereoisomer thereof for the preparation of a medicament for the treatment of alcoholism.

2. Pharmaceutical compositions for the treatment of alcohol addiction and withdrawal syndrome, containing baclofen or any stereoisomer thereof as the active principle.

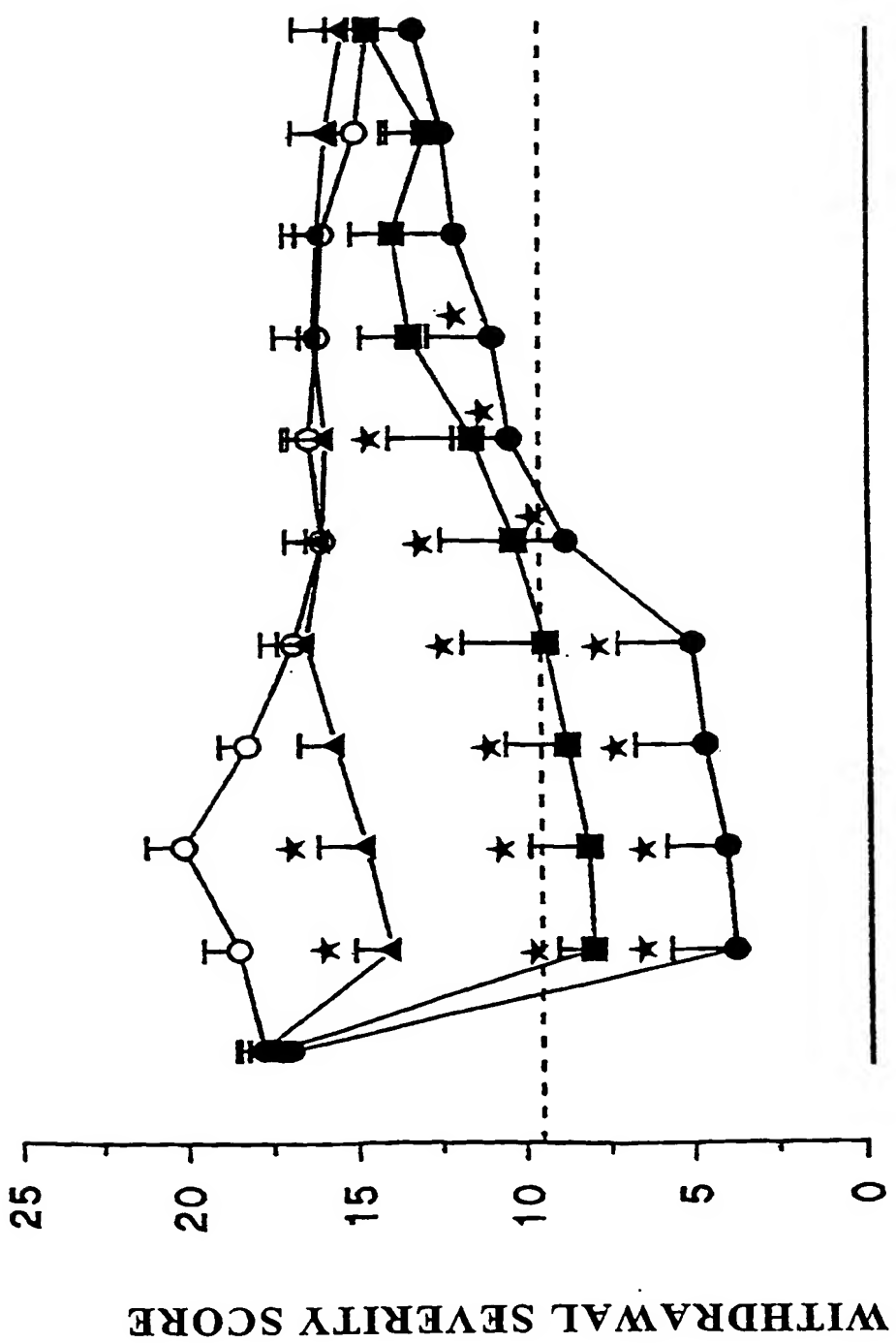
WITHDRAWAL SEVERITY SCORE
25
20
15
10
5
0
Pre
1
2
3
4
5
6
7
8
9
10
HOURS AFTER DRUG ADMINISTRATION

FIG. 1

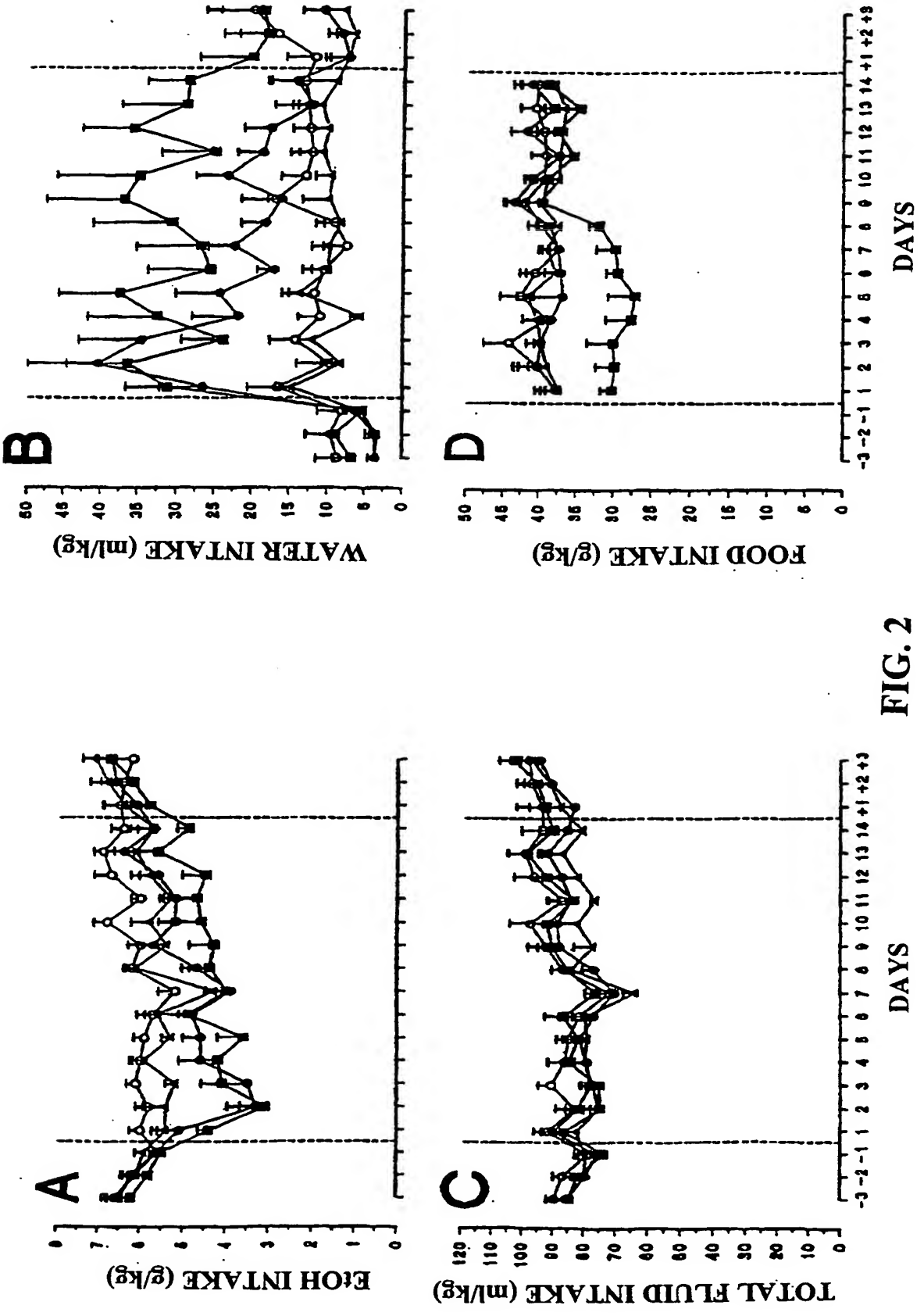
A
B
C
D
EtOH INTAKE (g/kg)
WATER INTAKE (ml/kg)
TOTAL FLUID INTAKE (ml/kg)
FOOD INTAKE (g/kg)
DAYS
DAYS

FIG. 2